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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

426A

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

JAN 4 1983

MEMORANDUM

SUBJECT: PP#2F2711/FAP#2H5357 Ethephon. Amendment of 12/6/82.

FROM: Raymond J. Kent, Chemist
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

TO: Robert Taylor, Product Manager #25
Fungicides/Herbicides Branch
Registration Division (TS-767)

THRU: Charles L. Trichilo, Chief
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

In response to our requests (see reviews for PP #'s 9F2178, 0F2312, and 2F2711) for a large animal metabolism study to support uses of ethephon (2-chloroethyl phosphonic acid) on major feed items, Union Carbide Agricultural Products Company, Inc. has submitted a lactating goat metabolism study (Accession #071263). Some of the results of the study (analyses of milk and tissues for residues of monochloracetic acid) were reported in an earlier petition (PP #0F2312).

Conclusions and Recommendations:

The metabolism study is inadequate because less than 15% of the administered radiolabel was accounted for, and radiolabeled residues in milk and liver were not identified. The study should be repeated with provisions made to collect CO_2, and radiolabeled residues in milk and liver should be characterized.

The deficiencies outlined in our previous review remain unresolved.

We continue to recommend against the proposed tolerance for the reasons cited in our previous review.

Detailed Considerations

A lactating goat was administered an average of 63 mg of 1,2-^{14}C-ethephon per kg of feed (range: 40-77 ppm) for a 10-day period. Milk, urine, and feces were collected daily during the treatment period, and tissues were collected at sacrifice, 24 hr after the last dose. All samples were frozen until analysis. Samples were analyzed for total ^{14}C by standard liquid scintillation techniques.

Distribution and recovery of administered radiocarbon is summarized in the following table:

SAMPLE	% OF DOSE	CONCENTRATION (ppm ethephon equivalents)
Urine	9.07	
Feces	2.67	
Milk	1.49	0.53-2.54; avg. 1.9, days 2-10
Tissues	1.41	
-Liver		5.25
-Mammary Glands		1.68
-Heart		1.38
-Brain		1.06
-Tenderloin		0.65
-Leg Muscle		0.59
-Rumen Contents		0.29
-Omental Fat		0.13
-Perirenal Fat		0.05

The metabolism study as submitted is inadequate. Less than 15% of the administered radiocarbon was recovered, the authors assuming that the balance was degraded to CO_2 by rumen fluid. No attempt was made to identify radiolabeled compounds in milk, tissues, or excretory products.

To support the contention that ethephon is extensively degraded to CO_2 in the rumen, the study should be repeated with provisions made for collection of evolved $^{14}CO_2$. In addition, because the present study demonstrates that residues resulting from a dietary intake of 60 ppm are as high as 2.5 ppm ethephon equivalents in milk and 5.2 ppm in liver, it will be necessary to characterize these residues. Feeding studies submitted earlier (PP #'s 3F1325, and 0F2312 or 2F2711) and data submitted with PP #0F2312 indicate that ethephon *per se* and monochloracetic acid could not be significant components of the residue. The milk and tissue residues may be the result of incorporation of $^{14}CO_2$ or other small carbon fragments into natural biochemical constituents. To demonstrate this point, it will be necessary to isolate some of these constituents and determine their radioactivity level.

cc: RF, Circu, Reviewer, FDA, PP#2F2711, TOX, EEB, EFB, Robert E. Thompson
RDI: RSQ; 12/29/82: RDS, 12/29/82
TS-769: RCB: R.Kent:X77484:CM#2:RM810:12/28/82

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

DEC 7 1982

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PP #2F2711/FAP #2H5357, (Including Amendment of 8/30/82). Ethephon on Wheat and Barley. Evaluation of Analytical Methods and Residue Data.

FROM: Raymond J. Kent, Chemist
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

TO: Robert Taylor, Product Manager #25
Fungicides/Herbicides Branch
Registration Division (TS-767)

THRU: Charles L. Trichilo, Chief
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

Union Carbide Agricultural Products Co., Inc. proposes that tolerances be established for residues of the plant growth regulator, ethephon [(2-chloroethyl)phosphonic acid] in or wheat and barley grain at 1 ppm, and wheat and barley straw at 10 ppm; and that food additive tolerances of 5 ppm be established for residues of ethephon in milled fractions of wheat and barley grain. The tolerances would provide for the use of ethephon as an antilodging agent on wheat and barley.

The permanent tolerances would replace temporary tolerances of 2 ppm for wheat and barley grain, 10 ppm for wheat and barley straw, and 5 ppm (food additive tolerance) for milled fractions (except flour) of wheat and barley. The temporary tolerances expire on 4/20/84.

Permanent tolerances varying from 0.1 to 30 ppm have been established for residues of ethephon on various RAC's (40 CFR §180.300). Permanent food additive tolerances have been established for raisins (12 ppm, 21 CFR §193.186), and raisin waste (65 ppm, 21 CFR §561.225).

Conclusions

1. TOX should be informed that technical ethephon contains up to [redacted] We estimate that residues of [redacted] resulting from the proposed use will not exceed [redacted] on barley or wheat grain immediately after application of 0.5 lb-ethephon per acre.

2(a). The nature of the residue in wheat and barley is adequately understood. The residue of concern consists of ethephon per se.

2(b). The fate of ethephon in food-producing animals is not known. A large animal metabolism study, such as the ^{14}C-ethephon lactating goat study that was to be submitted with PP #'s 9F2178 and 0F2312, is required.

3(a). Analytical methods for grain, straw, and milk submitted with this petition are adequate for obtaining residue data.

3(b). The residue method for meat and meat by-products submitted in conjunction with a dairy cow feeding study (150 ppm maximum dose) is inadequate because of insensitivity and variability of control samples. When the metabolism of ethephon in food-producing animals is defined, methods capable of determining the residue of concern at sensitivities of 0.01-0.05 ppm should be submitted. The methods sensitive to 0.01 ppm submitted with PP #3F1325 would be considered suitable for this purpose if ethephon is shown to be the sole residue of concern in food-producing animals. The methods submitted for both meat and milk should not be stamped 'Confidential' or 'Trade Secret' since they will be subjected to a method trial and published in PAM II.

3(c). Method I for ethephon in PAM II is satisfactory for enforcement of grain tolerances.

3(d). We are unable to conclude that Method I in PAM II is suitable for enforcement of straw tolerances. Method I lacks a cleanup step contained in the residue method, and thus straw samples analyzed by Method I may appear to contain over-tolerance residues. The petitioner should use Method I in PAM II to reanalyze control and treated straw samples to determine whether the method is adequate for tolerance enforcement. If Method I is not adequate, a method trial of the residue method for straw will be necessary.

4(a). The proposed antilodging use of ethephon on wheat and barley is unlikely to result in residues in excess of the proposed tolerance for grain, straw, and milled grain fractions. The food additive regulation when published should be in terms of "milling fractions (except flour)".

4(b). In the absence of residue data, there should be a label restriction against the grazing, feeding, or cutting for hay of ethephon-treated wheat and barley.

4(c). Because of inadequate metabolism data, we are unable to categorize feed uses of ethephon under 40 CFR §180.6(a). If ethephon per se is subsequently shown to be the sole residue of concern, we would be able to make the following conclusions:

I. Uses with respect to poultry and eggs would fall in category (3), and no tolerances would be required; and

II. Uses with respect to milk would fall in category (2). A tolerance proposal would be required with 0.02 ppm being an appropriate level.

Because the latest cattle feeding study is inadequate for reasons of methodology as well as metabolism, we would still be unable to categorize feed uses with respect to meat, fat and meat by-products even if the metabolism in animals were known. When the metabolism of ethephon in food-producing animals is established, meat, fat and meat by-product samples from the feeding study should be reanalyzed by appropriate methods sensitive to 0.01-0.05 ppm (see Conclusion 3b).

5. Because ethephon is not used on wheat and barley outside of the United States, there is no problem with compatibility of international tolerances. A Residue Limit Sheet is attached.

Recommendations

We recommend against the proposed tolerances because of conclusions 2b, 3b, 3d, 4b, and 4c.

Detailed Considerations

Manufacturing Process

[redacted]

Composition of Technical Ethephon

[redacted]

TOTAL	100.00%

We have deferred to TOX on several occasions concerning the [redacted] in technical ethephon, and have provided them with worst case estimates of residues of [redacted] in a variety of crops. For wheat and barley, this estimate is as follows:

[redacted]

We defer to TOX with regard to any concern they may have over possible residues of [redacted] in wheat or barley grain.

Formulations

CERONE-2 Plant Regulator containing 2 lb ai/gallon is equivalent to ETHREL Plant Regulator (EPA Reg. No. 264-267). CERONE-4 Plant Regulator containing 4 lb ai/gallon is equivalent to ETHREL Pineapple Regulator (EPA Reg. No. 264-257). Both products are prepared from technical ethephon [redacted].

Proposed Use

To prevent lodging in barley and wheat, ethephon is applied once per season as a foliar spray at 0.25 to 0.5 lb active ingredient in 3 to 25 gallons of water per acre. To achieve its antilodging effect, the growth regulator must be applied between the early boot stage when the flag leaf is just visible, to the late boot stage when the ear is swollen but not yet visible.

Nature of the Residue

No data on the nature of the residue in ethephon-treated wheat and barley were submitted with this petition.

Numerous studies on the fate of ^{14}C-ethephon in crops have been submitted with earlier petitions (cf. reviews for PP #'s 1F1016, 1G1172, 2G1195, 2G1217, and 2F1275). In plants, ethephon is readily absorbed, partially translocated, and degraded to ethylene, inorganic phosphate, and chloride ion. The only residue detected in crops is the parent compound.

^{14}C-Ethephon studies in animals have been limited to rats (3/9/72 review of J. M. Worthington; PP #2G1195) and cow tissues (2/1/73 review of M. J. Nelson; PP #3F1325). In both systems, ethephon and ethylene were the only compounds detected.

Heretofore, ethephon has not been used on major feed items and we have not required a large animal metabolism study. Because the present petition involves permanent tolerances on major feed items, we require that a large animal metabolism study be performed. A ^{14}C-ethephon lactating goat study was in fact to be submitted by Union Carbide in conjunction with PP #'s 9F2178 and 0F2312, but the study has not yet been received.

We conclude that the fate of ethephon in plants is adequately understood, but the fate in animals is not yet defined.

Analytical Methods

Grain and milled grain fractions were analyzed by a GLC method originally submitted with PP #1F1016. Freeze dried samples are Soxhlet extracted with methanol. The extract is acidified with methanolic HCl, concentrated, treated with diethyl ether to precipitate interferences, and treated with diazomethane to convert ethephon to its dimethyl ester. The derivative is analyzed on columns equipped with a flame photometric detector in the phosphorus mode. Sensitivity of the method is 0.02 ppm. Recovery of ethephon from 20 grain samples fortified at 0.2 ppm averaged 95% (range = 66-141%; standard deviation = 20%).

Straw was analyzed by a similar method except that an additional Florisil column cleanup is used after esterification with diazomethane. Sensitivity of the method is estimated to be 0.05 ppm. Recovery of ethephon from 11 samples fortified at 0.2 ppm averaged 92% (range = 70-129%; standard deviation = 20%).

Methods similar to the method for grain described above have been used for the analysis of residues in milk, fat, muscle, and liver of dairy cattle (2/1/73 and 6/11/73 reviews of M. J. Nelson; PP #3F1325), and for the analysis of residues in poultry and eggs (1/20/75 review of A. Smith; PP #5F1524). Sensitivity of the methods for eggs, poultry tissues, and cattle tissues is 0.01 ppm. Sensitivity of the method for milk is 0.1 ppm.

GLC methods for milk and cattle tissues were recently submitted in conjunction with a high dose feeding study (6/18/82 review of R. Loranger; this petition and PP #0F2312). Sensitivities of the methods, which differ considerably from the earlier meat and milk methods, are claimed by the petitioner to be 0.1 ppm for muscle, 0.2 ppm for liver, fat, heart, and kidney, and 0.05 ppm for milk. Representative chromatograms (Amendment of 8/30/82) submitted in response to our request (6/18/82 review of R. Loranger) for all chromatograms of control, fortified, and treated milk and tissue samples from the feeding study, indicate that the method for cattle tissues is unreliable for obtaining quantitative residue data. Control values are variable and the ethephon peak is usually a small shoulder on the sharp downslope of a larger peak. We estimate that the limit of detectability for cattle tissues is 0.2-0.3 ppm. For milk, the limit of detectability is between 0.05 and 0.1 ppm.

For enforcement of wheat and barley grain tolerances, PAM II contains a method (Method I) for the determination of ethephon in pineapple that is nearly identical to the grain residue method. The confirmatory method for pineapple (Method A, PAM II) should also be satisfactory for grains.

We are unable to conclude that the methods in PAM II are suitable for enforcement analyses of straw. Although the residue method for straw is similar to PAM II methods, the residue method contains an additional cleanup step following esterification with diazomethane. Since straw analyzed without the additional cleanup may appear to have over-tolerance residues, we ask the petitioner to reanalyze treated and control straw samples using Method I in PAM II; otherwise a trial of the straw residue method will be necessary.

Enforcement methods sensitive to 0.01-0.05 ppm for milk, and for meat, fat and meat by-products, will be necessary. Method trials will be initiated when copies of methods not marked 'Trade Secret' or 'Confidential' are sent by the petitioner.

Residue Data

Residues in grain and straw. Data representative of numerous wheat and barley growing areas and reflecting 1 to 1.5x the maximum proposed treatment rate are summarized in the following table: (some of the data were included in PP #2G2619)

RESIDUE SUMMARY

SAMPLE	Rate (lb/acre)	PHI (days)	RESIDUE LEVELS (ppm)			
			<0.1	0.1-0.5	0.5-1.0	>1.0
Wheat grain	0.5-0.75	41-64	38	15	0	0
Barley grain	0.5-0.75	41-64	12	11	4	1
			<1.0	1.0-5.0	5.0-10.	>10.
Wheat straw	0.5-0.75	41-68	15	13	3	0
Barley straw	0.5-0.75	41-68	5	3	0	0

The petitioner claims that one value of 1.42 ppm for barley grain is statistically aberrant at the 99% confidence level. We are inclined to agree with that assessment. The sample is 1 of 4 replicates, the other samples containing 0.02, 0.07, and 0.08 ppm ethephon. The next highest values, 4 replicates of barley grain from a plot treated at 0.5 lb per acre, were 0.79 (2), 0.78, and 0.75 ppm. No other sample of wheat or barley grain contained residues in excess of 0.5 ppm.

We conclude that residues on wheat and barley grain and straw are unlikely to exceed the proposed tolerance as a result of the antilodging use.

There are no residue data for forage or hay of wheat and barley, and no label restrictions against grazing livestock on the treated crops. Although the use of the growth regulator is such that livestock are unlikely to be grazed on treated forage, a label restriction against grazing or feeding livestock on treated barley and wheat forage and hay is nevertheless required.

Residues in milling fractions. Grain fractionation studies were submitted with PP #2G2619 (5/28/82 review of W. L. Anthony). Concentration of residues was observed in all fractions except flour, and varied from 1.6 to 3.5x.

We conclude that the proposed 5 ppm food additive tolerance for milling fractions of wheat and barley is appropriate; however, the regulation when published should be in terms of "milling fractions (except flour)".

Residues in meat, milk, poultry, and eggs. We estimate that if feed items with ethephon tolerances are combined to form a cattle diet, the level of ethephon in the diet would not exceed 15 ppm. Similarly we would not expect the level of ethephon in poultry diets to exceed 5 ppm.

When earlier (1973) dairy cow feeding study had indicated that a dietary intake of 20 ppm would not result in detectable amounts of ethephon in meat (<0.01 ppm) or milk (<0.1 ppm) (2/1/73 and 6/11/73 reviews of M. J. Nelson; PP #3F1325), a more recent study shows that transfer of ethephon to milk, and possibly to meat does occur at a feeding level of 150 ppm ethephon (6/18/82 review of R. Loranger;

this petition and PP #0F2312). Ethephon residues as high as 0.14 ppm was detected in milk of 3 cows receiving 150 ppm ethephon for 28 days, but was not detected at a feeding level of 50 ppm. Ethephon at the limit of detection (0.2 ppm) was found in liver of one of the cows dosed at 150 ppm. Ethephon was not detected in muscle (<0.1 ppm), heart (<0.2 ppm), kidney (<0.2 ppm), or fat (<0.2 ppm) of the cow with the positive liver sample, nor in any of the tissues of the other 2 cows receiving 150 ppm ethephon. Ethephon was not detected in liver or kidney of cows dosed at 50 ppm. As discussed under Analytical Methods, we do not consider the method used by the petitioner to obtain residue data on meat and meat by-products to be adequate, and thus the feeding study is inconclusive with respect to meat and meat by-products.

Ethephon was not detected in tissues or eggs of hens maintained for 28 days on a diet containing 25 or 50 ppm ethephon (1/20/75 review of A. Smith; PP #5F1524).

It should be noted that for all of the feeding studies carried out thus far, the residue of concern in food-producing animals has been assumed to be ethephon per se. To establish whether or not this assumption is corrrect, we are requiring a lactating ruminant metabolism study, and if new data results in the addition of metabolites to the regulated residue, then new feeding studies will be necessary. If ethephon were shown to be the only residue of concern, feed uses of ethephon would fall under category (3) of 40 CFR §180.6(a) with respect to poultry and eggs, and category (2) with respect to milk. A tolerance of 0.02 ppm for residues of ethephon in milk would be appropriate.

Because the latest cattle feeding study is inadequate for reasons of methodology as well as metabolism, we would still be unable to categorize feed uses with respect to meat, fat and meat by-products even if the metabolism in animals were known. When the metabolism of ethephon in food-producing animals is established, meat, fat and meat by-product samples from the feeding study should be reanalyzed by methods sensitive to 0.01-0.05 ppm. The methods sensitive to 0.01 ppm submitted with PP #3F1325 entitled "Detailed Method of Analysis for Residues of (2-Chloroethyl)-phosphonic Acid (Ethephon) in Cow Fat and Muscle Tissues" (dated 4/73), and "Detailed Method of Analysis for Residues of (2-Chloroethyl)phosphonic Acid (Ethephon) in Cow Liver Tissue" (dated 5/73) would be considered suitable for this purpose if ethephon is shown to be the sole residue of concern in food-producing animals.

Other Considerations

We have stated that a tomato processing study will be necessary before permanent tolerances can be granted on a major feed item (5/28/82 review of W. L. Anthony, PP #2G2619). Union Carbide has indicated that such a study is in their research plans, however, they request that the present petition not be delayed until the study is submitted.

We are inclined to go along with their request for the following reasons:

(1) There is no concentration of residues in feed items such as apple pomace (PP #3F1325), pineapple bran (PP #2G1195), and grape pomace (PP #9F2178) that are thermally processed like dried tomato pomace.

(2) Residues are detected in milk (and possibly meat) only at an exaggerated feeding level of 150 ppm ethephon, whereas current and proposed feed uses (exclusive of tomato pomace) will result in a maximum of 10-15 ppm in the animal diet. It is highly unlikely that any contribution to dietary ethephon from tomato pomace, even if there is some concentration of residues, will be so great that total ethephon approaches the exaggerated feeding level.

We do expect the processing study to be submitted upon completion. The study will almost certainly be required when the ethephon data base is reviewed under the Agency's reregistration program.

Because ethephon is not used on wheat and barley outside of the United States, there is no problem with compatibility of international tolerances. A Residue Limit Sheet is attached.

cc: RF
Circu
Reviewer
FDA
PP# No. 2F2711
TOX
EEB
EFB
Robert E. Thompson

RDI:Section Head:RSQ:Date 12/6/82
TS-769:RCB:Reviewer:R.Kent:R.Kent:Date:12/2/82

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL ETHEPHON PETITION NO 2E2711/2H5357

CCPR NO. none

Codex Status

[V] No Codex Proposal Step 6 or above

Proposed U. S. Tolerances

Residue (if Step 9): _____

Residue: ETHEPHON [(2-CHLOROETHYL) PHOSPHONIC ACID]

Crop(s)	Limit (mg/kg)

Crop(s)	Tol. (ppm)
BARLEY GRAIN	1
" STRAW	10
WHEAT GRAIN	1
" STRAW	10
MILLING FRACTIONS OF WHEAT & BARLEY	5

CANADIAN LIMIT

Residue: _____

Crop	Limit (ppm)
none (on above commodities)	

MEXICAN TOLERANCIA

Residue: _____

Crop	Tolerancia (ppm)
none	

Notes:

13544

038600

Chemical:	**Ethephon**
PC Code:	**099801**
HED File Code	**11000 Chemistry Reviews**
Memo Date:	**01/04/83**
File ID:	**00000000**
Accession Number:	**412-03-0113**

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